IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Hölzemann et al. Group Art Unit: 1653

Serial No.: 09/486,062 Examiner: D. Lukton

Filed: 05/05/00

For: Cyclopeptide Derivatives

DECLARATION UNDER 37 C.F.R. § 1.132

Honorable Commissionar of
Patents and Trademarks
Washington, D.C. 20231

SIR:

Simon L. Goodman, being duly warned, deposes and says:

I am a citizen of Great Britain residing at Darmstadt, Germany;

I am a biochemist by training and experience;

the degree of D. Phil. was bestowed on me by the University of Sussex, Brighton, Great Britain in 1977;

from 1977 to 1979 I was employee at Comshare Ltd., London, Great Britain;

from 1979 to 1982 I was scientist at the Imperial Cancer research Fund, London, Great Britain;

from 1982 to 1986 I was scientist at the Max Planck Institute, Tübingen, Germany;

from 1986 to 1989 I was scientist at the Max Planck Institute, Martinsried, Germany;

from 1989 to March 1993 I was scientist at the Max Planck Institute, Erlangen, Germany;

since April 1993 I am Head of a biochemical laboratory of Merck KGaA, Darmstadt, Germany;

I am author or co-author of numerous papers and patents in the fields of biochemistry and cell biology.

The test results presented below for the present application prove that the claimed compounds are inhibitors of integrin $\alpha_V\beta_3$.
I have carried out, or supervised experiments for testing the receptor inhibition according to the methods described within the genus claimed in the pending application.

Pharmacological Report

Receptor Inhibition assay

Purified human integrins $\alpha_v\beta_3$ from term placenta were adsorbed to microtitre wells and challenged with biotinylated complementary ligands - vitronectin (VN) for $\alpha_v\beta_3$ in the presence of increasing amounts of test compounds.

Method: 1 μg ml^{-1} biotin-ligand was incubated with 1 μg ml^{-1} coated receptor in the presence of serially diluted peptides. After 3 h at 30° C bound ligand was measures by anti-biotin - alkaline phosphatase detection.

Literature: Charo, I.F., Nannizzi, L., Smith, J.W. and Cheresh, D.A., J. Cell. Biol. **111**, 2795-2800 (1990).

The test data of the Pharmacological Report (Table I) show the compounds tested and their IC_{50}-values.

Table I

IC_{50} values for binding of biotinylated ligands to human placental $\alpha_v\beta_3$.

code	compound page/line	IC_{50} [M]
		VN: $\alpha_v\beta_3$
EMD 157604	23/22-25 (example 1)	2.80E-09
EMD 130187	24/8-11 (example 2)	7.70E-09
EMD 130186	24/19-23 (example 3)	2.90E-08

The compounds tested exhibit inhibitory activity on $\alpha_v\beta_3$ vitronectin interaction.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1 June 2001
Date

Simon Goodman